Inorg. Chem. **2007**, *46*, 4733–4736

A Novel Asymmetric Hydroarsination Reaction Promoted by a Chiral Organopalladium Complex

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Received January 29, 2007

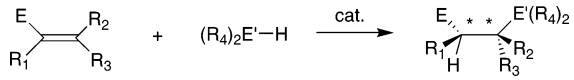
The dissymmetrical chiral bidentate (*R*)-(+)-1-(diphenylphosphino)-2-(diphenylarsino)propane was prepared stereoselectively via the novel asymmetric hydroarsination reaction between diphenylarsine and diphenyl-1-propenyl-(*E*)-phosphine using di-μ-chlorobis{(*S*)-1-[1-(dimethylamino)ethyl]-2-naphthalenyl-*C*,*N*}dipalladium(II) as the chiral reaction promoter.

Introduction

The asymmetric addition reaction between an E−H (i.e., E = N, P) moiety of an amine or phosphine and a C−C double bond of an unsaturated compound is one of the most important reactions in producing N- or P-containing chiral compounds (Scheme 1).[1] As early as 1961, Stern and Spector investigated the addition reaction involving N−H using palladium(II) complexes as the catalysts.[2] However, it was not until recently that these reactions were being applied to the asymmetric synthesis of chiral molecules.[3,4] These reactions are mostly promoted by organometallic reagents comprising transition metals and chiral auxiliaries.

Reports on metal-ion-promoted asymmetric hydroamination have shown that it may proceed along two different pathways. The first pathway involves the oxidative addition of the N−H bond onto the metal ion followed by insertion of the olefin and finally reductive elimination of the chiral product.[3] The second pathway involves a nucleophilic reaction between a coordinated olefin on the chiral metal promoter and the free amine, followed by protonolysis to release the final product.[4] There are also reports on intramolecular asymmetric hydroamination of aminoolefins forming chiral pyrrolidines and piperidines using chiral organolanthanide complexes.[5] Recently, we have reported the asymmetric synthesis of a P chiral iminophosphine via the metal-ion-promoted asymmetric hydroamination reaction between aniline and bis(phenylethynyl)phenylphosphine.[6]

Scheme 1



The analogous asymmetric hydrophosphination is relatively new but has rapidly become a potentially effective synthetic strategy for the preparation of chiral phosphines, which are useful as ligands in asymmetric synthesis and biological studies.[7] Similar to the hydroamination reaction, two types of reaction mechanisms have been reported for the metal-ion-induced hydrophosphination reaction: Glueck and co-workers observed the oxidative addition of a secondary phosphine followed by olefin insertion[8] while Togni's group observed the coordination of the olefin followed by the addition of a secondary phosphine across the C−C double

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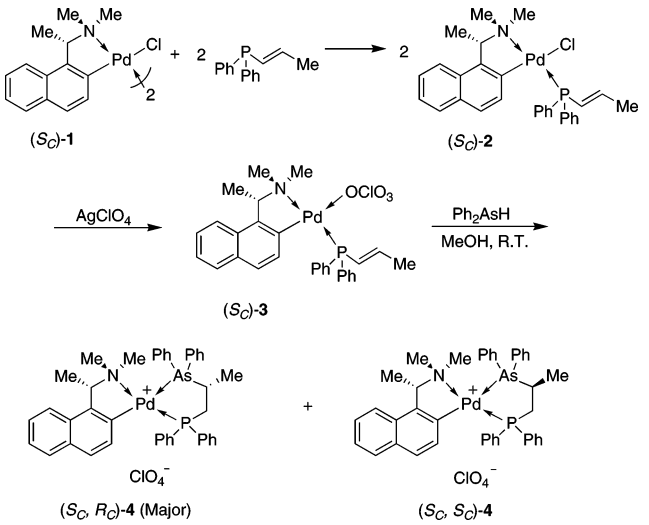
10.1021/ic0701561 CCC: $37.00
Published on Web 04/26/2007

Scheme 2



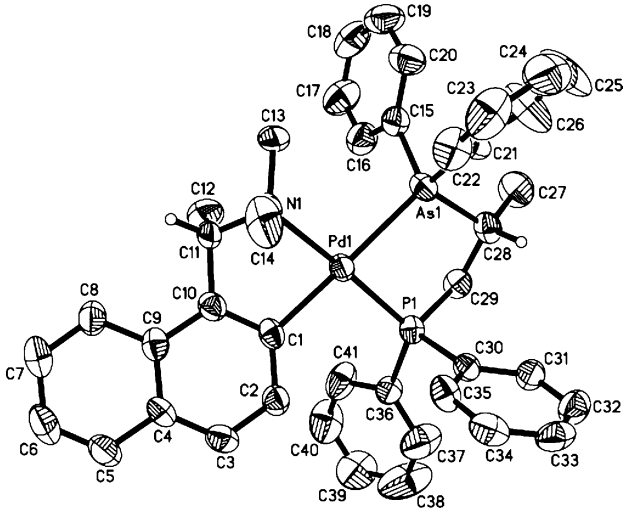


Figure 1. Molecular structure of the cationic complex (S_C,R_C)-**4**.

bond.[9] On the other hand, it has been shown that the asymmetric hydrophosphination of vinylic phosphines involves the simultaneous coordination of both the reacting vinylic phosphine and the secondary phosphine on the chiral metal complex.[10] We have recently reported the synthesis of prophos with high enantioselectivity via an asymmetric hydrophosphination reaction.[10b]

Today, asymmetric hydroamination can be employed for the routine synthesis of chiral amine compounds[11] while the corresponding hydrophosphination reaction provides an alternative way of preparing chiral organophosphorus compounds.[8−10] Nevertheless, the number of reports on the addition of the As−H moiety to C=C or C≡C bonds is few.[12] Certainly no asymmetric syntheses involving As−H bond activation have been reported hitherto. Such a process should generate potentially powerful and stereospecific arsenic chelating agents for synthetically important second- and third-row transition metals. In this paper, we report the synthesis of an optically active P−As heterobidentate ligand via the first asymmetric hydroarsination reaction.

Results and Discussion

In the absence of a metal ion, no reaction was observed between diphenylarsine and vinylphosphines. Thus, the monodentate (*E*)-propenyldiphenylphosphine was coordinated to the dimeric chiral template (S_C)-**1** via a regiospecific bridge-splitting process (Scheme 2).[13] It is important to note that the chloro ligand in the template complex (S_C)-**2**[13] and in similar complexes is well-known to be kinetically and thermodynamically stable and is not readily displaced by other strong ligands such as monodentate phosphines[10] and amines.[6] In order to provide a coordinate site for the reacting diphenylarsine, (S_C)-**2** was treated with silver perchlorate prior to the introduction of the secondary arsine into the reaction mixture. The asymmetric hydroarsination reaction was monitored by ^{31}P NMR spectroscopy and was found to proceed in a facile manner in methanol at room temperature and completed within 24 h. Only two diastereomeric complexes, (S_C,R_C)-**4** and (S_C,S_C)-**4**, were generated with a diastereoselectivity of 8:1. While the addition of the secondary phosphine resulted in cis−trans regioisomers of the products,[10b] the addition of diphenylarsine in this case is 100% regioselective, wherein the P atom occupies the coordination site trans to N. The high regioselectivity observed in the present case is in agreement with what has been observed for similar Ar−P heterobidentate ligands.[14] No other products were detected by 202 MHz ^{31}P NMR spectroscopy. The two diastereomeric products could be separated into their stereoisomerically pure forms by fractional recrystallization from dichloromethane−diethyl ether. The less soluble major isomer, (S_C,R_C)-**4**, was isolated as colorless square plates in 34% yield: $[\alpha]_D$ +56.8 (*c* 0.2, CH_2Cl_2). The ^{31}P NMR spectrum of (S_C,R_C)-**4** in $CDCl_3$ exhibited a singlet at δ 51.4. The crystallization of the more soluble minor isomer, (S_C,S_C)-**4**, was less effective, and it was isolated only in 6% yield as colorless microprisms with $[\alpha]_D$ +64.0 (*c* 0.1, CH_2Cl_2). The ^{31}P NMR spectrum of this minor product in $CDCl_3$ exhibited a singlet at δ 51.2.

The molecular structure and the absolute stereochemistry of the major product (S_C,R_C)-**4** were determined by single-crystal X-ray diffraction analysis. There are two crystallographically distinguished molecules in the asymmetric unit with slightly different bond lengths and angles. Figure 1 shows the ORTEP drawing of molecule 1. Selected bond lengths and angles are listed in Table 1. The coordination

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Table 1. Selected Bond Lengths (Å) and Angles (deg) for Complex (S_C,R_C)-**4**

Pd1−C1	2.051(5)	C1−Pd1−N1	80.4(2)
Pd1−N1	2.144(5)	C1−Pd1−P1	97.0(1)
Pd1−P1	2.255(2)	N1−Pd1−P1	177.3(2)
Pd1−As1	2.484(1)	C1−Pd1−As1	177.2(2)
As1−C21	1.936(3)	N1−Pd1−As1	99.5(2)
As1−C15	1.948(6)	P1−Pd1−As1	83.1(1)
As1−C28	1.983(6)	C29−P1−Pd1	109.2(2)
P1−C30	1.809(5)	C28−As1−Pd1	107.1(1)
P1−C36	1.821(6)	C27−C28−C29	112.0(5)
P1−C29	1.824(5)	C27−C28−As1	116.6(5)
C27−C28	1.511(8)	C29−C28−As1	106.4(4)
C28−C29	1.541(8)	C28−C29−*P*1	114.0(4)

geometry about Pd correlates with data on all previous complexes containing the ortho-metalated dimethyl[1-(α-naphthyl)ethyl]amine ring:[10b] The five-membered organometallic ring containing the Pd atom has an asymmetric skew conformation of λ helicity, with the methyl substituent on the asymmetric C stereogenic center of *S* absolute configuration occupying the *axial* site. The P and As donor atoms of the new heterobidentate are bonded regiospecifically to the Pd atom, with the softer P donor taking up the position trans to the NMe_2 group. In contrast to the organometallic ring, the new As−P bidentate chelate adopts the asymmetric skew conformation of λ helicity, with the methyl substituent on the asymmetric C28 stereocenter of *R* absolute configuration occupying the sterically favorable *equatorial* position. All of the substituents at C28 and the bulky As−Ph groups adopt a staggered orientation. The interchelate steric repulsion between the NMe_2 and $AsPh_2$ groups is reflected clearly by the larger N1−Pd1−As1 angle [99.5(2)°] as compared with the smaller C1−Pd1−P1 angle [97.0(1)°]. The Pd1−As1 bond distance [2.48(1) Å] is significantly longer than the Pd1−P1 bond distance [2.25(1) Å]. The C28−C29 bond distance [1.54(1) Å] is inconsistent with a typical C−C single bond.

It is noteworthy that the current asymmetric hydroarsination reaction could only be induced effectively in polar solvents, such as methanol. The reaction failed when nonalcoholic or nonpolar solvents, such as dichloromethane and benzene, were employed. From a mechanistic standpoint, the simultaneous coordination of diphenylarsine and methyl-substituted vinylphosphine on the chiral palladium template polarizes the As−H and vinylic C═C bonds concurrently. An intermediate involving the deprotonated form of the highly reactive coordinated arsenido ligand could be generated. This highly reactive nucleophile can be stabilized by the polar solvent, which promotes the nucleophilic addition reaction to form the new As−C bond. Furthermore, an alcoholic solvent would facilitate in the subsequent protonolysis process in this metal-complex-promoted hydroarsination reaction. Indeed, the protonolysis of the P−C carbon may be initiated by the proton of the methanol solvent, which may be regenerated subsequently by proton transfer from the As−H moiety. A similar stepwise proton-transfer process involving a coordinated secondary phosphine has been described previously.[15]

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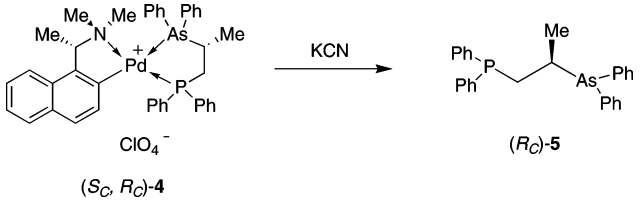
Scheme 3



The new As−P chiral bidentate generated in the hydroarsination reaction could be liberated efficiently from the chiral metal template (Scheme 3). Treatment of the palladium template (S_C,R_C)-**4** with aqueous potassium cyanide gave the optically pure (+)-1-(diphenylphosphino)-2-(diphenylarsino)-propane (R_C)-**5** as a moderately air-sensitive colorless oil in 90% yield: $[\alpha]_D = +131.0$ (*c* 0.2, CH_2Cl_2). The ^{31}P NMR spectrum of (R_C)-**5** in $CDCl_3$ exhibited a singlet at δ −20.5. The liberated ligand could be recoordinated back to the same metal template without loss of optical purity.

In summary, we have demonstrated that transition-metal-complex-promoted asymmetric hydroarsination is a potential synthetic route for the preparation of asymmetric arsenic ligands. We are currently investigating if these asymmetric addition reactions can be applied to other unsaturated moieties containing reactive organic functional groups.

Experimental Section

All air-sensitive manipulations were carried out using Schlenk and cannula techniques under a positive pressure of argon. All NMR spectra were recorded at 25 °C on Bruker ACF 300 and 500 MHz spectrometers. Optical rotations were measured on the specified solution in a 1 dm cell at 25 °C with a Perkin-Elmer model 341 polarimeter. Elemental analyses were performed by the staff in the Elemental Analysis Laboratory of the Division of Chemical and Biological Sciences of Nanyang Technological University. All melting points were measured using the SRS Optimelt Automated Melting Point System, SRS MPA100.

All solvents used for the synthesis of ligands and reactions were deoxygenated using a positive pressure of argon. Analytical-grade chemicals were purchased from Sigma-Aldrich and Strem Chemicals. The chiral palladium complexes (S_C)-**1**[16] and (S_C)-**2**[13] and the tertiary phosphine (*E*)-propenydiphenylphosphine[17] were prepared according to literature methods.

Caution! *All perchlorate salts should be handled as potentially explosive compounds. Care should be taken in handling highly toxic arsine and cyanide compounds.*

Hydroarsination Reaction. Isolation of {(*S*)-1-[1-(dimethylamino)ethyl]-2-naphthyl-*C,N*][(*R/S*)-1-(diphenylphosphino)-2-(diphenylarsino)propane-*P,As*}palladium(II) Perchlorate, (S_C,S_C/R_C)-4. A solution of (S_C)-**2** (0.25 g) in dichloromethane (50 mL) was treated with silver perchlorate (0.46 g) in water (5 mL). The solution was stirred for 1 h at room temperature. The white precipitate, silver chloride, was filtered off using Celite. The solution was subsequently washed with water (3 × 30 mL), and then the organic layer was dried over magnesium sulfate. The solvent was removed, and the yellow solid was redissolved in methanol (150 mL). This solution was treated with diphenylarsine (0.10 g) dissolved in methanol (10 mL). The reaction was stirred at room

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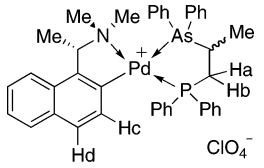
Table 2. X-ray Crystallographic Data of (S_C,R_C)-**4**

formula	$C_{41}H_{42}AsClNO_4PPd\cdot0.5CH_2Cl_2$
fw	902.96
space group	*P*2(1)
cryst syst	monoclinic
a/Å	19.4261(9)
b/Å	9.7061(4)
c/Å	22.1846(10)
α/deg	90
β/deg	106.477(2)
γ/deg	90
V/Å^3	4011.2(3)
Z	4
T/K	298(2)
ρ_{calcd}/g cm^{-3}	1.495
μ/mm^{-1}	1.496
λ/Å	0.710 73
Flack parameters	−0.012(9)
R1 (obsd data)[a]	0.0537
wR2 (obsd data)[b]	0.1003

[a] $R1 = \sum||F_o| - |F_c||/\sum|F_o|$. [b] $wR2 = \{\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]\}^{1/2}$, $w^{-1} = \sigma^2(F_o)^2 + (aP)^2 + bP$.

temperature for 24 h. The crude product was monitored by ^{31}P NMR until no more starting material was present. Two new signals were observed at δ 51.17 and 51.44 with a relative intensity of 1:8. Methanol was removed from the reaction pot, and the crude product was redissolved in dichloromethane until the solution was saturated. The two products were separated by slow recrystallization using diethyl ether. The major isomer, (S_C,R_C)-**4**, crystallized as colorless square plates: 0.13 g (34% yield). $[\alpha]_D$: +56.8 (*c* 0.2, CH_2Cl_2). Mp: 210−211 °C (dec). Anal. Calcd for $C_{41}H_{42}AsClNO_4PPd\cdot0.5CH_2Cl_2$: C, 55.2; H, 4.8; N, 1.6. Found: C, 54.8; H, 4.8; N, 1.6. ^{31}P NMR ($CDCl_3$): δ 51.4 (s). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.22 (d, 3H, $^3J_{H-H}$ = 6.6 Hz, AsCH*Me*), 2.03 (d, 3H, $^3J_{H-H}$ = 6.3 Hz, CH*Me*), 2.14 (dt, 1H, $^2J_{H-P,H}$ = 14.4 Hz, $^3J_{H-H}$ = 5.7 Hz, PC*H*$_a$H$_b$), 2.40−2.50 (br m, 1H, AsC*H*Me), 2.70 (s, 3H, N*Me*$_{ax}$), 2.90 (d, 3H, $^4J_{P-H}$ = 3.6 Hz, N*Me*$_{eq}$), 3.06 (dt, 1H, $^2J_{H-P,H}$ = 14.1 Hz, $^3J_{H-H}$ = 4.2 Hz, PCH$_a$*H*$_b$), 4.56 (qn, 1H, $^3J_{H-H}$ = $^4J_{P-H}$ = 6.3 Hz, C*H*Me), 6.86 (dd, 1H, $^3J_{H-H}$ = 8.40 Hz, $^4J_{P-H}$ = 5.70 Hz, H$_c$), 7.08 (d, 1H, $^3J_{H-H}$ = 8.7 Hz, H$_d$), 7.33−7.83 (m, 22H, aromatics), 8.24 (dd, 2H, $^3J_{H-H}$ = 6.0 Hz, $^3J_{P-H}$ = 6.50 Hz, *O*Ph). After isolation of the major isomer, the minor isomer (S_C,S_C)-**4** subsequently crystallized from the concentrated mother liquor as colorless microplates: 0.02 g (6% yield). $[\alpha]_D$: +64.0 (*c* 0.1, CH_2Cl_2). Mp: 211−212 °C (dec). Anal. Calcd for $C_{41}H_{42}AsClNO_4PPd\cdot0.5CH_2Cl_2$: C, 55.2; H, 4.8; N, 1.6. Found: C, 54.8; H, 5.0; N, 1.6. ^{31}P NMR ($CDCl_3$): δ 51.17 (s). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.20 (d, 3H, $^3J_{H-H}$ = 6.5 Hz, AsCH*Me*), 2.01 (d, 3H, $^3J_{H-H}$ = 6.0 Hz, CH*Me*), 2.12 (dt, 1H, $^2J_{H-P,H}$ = 14.50 Hz, $^3J_{H-H}$ = 5.5 Hz, PC*H*$_a$H$_b$), 2.35−2.45 (br m, 1H, AsC*H*Me), 2.68 (s, 3H, N*Me*$_{ax}$), 2.88 (d, 3H, $^4J_{P-H}$ = 4.0 Hz, N*Me*$_{eq}$), 3.04 (dt, 1H, $^2J_{H-P,H}$ = 14.12 Hz, $^3J_{H-H}$ = 3.80 Hz, PCH$_a$*H*$_b$), 4.54 (qn, 1H, $^3J_{H-H}$ = $^4J_{P-H}$ = 6.25 Hz, C*H*Me), 6.84 (dd, 1H, $^3J_{H-H}$ = 8.50 Hz, $^4J_{P-H}$ = 5.50 Hz, H$_c$), 7.06 (d, 1H, $^3J_{H-H}$ = 9.0 Hz, H$_d$), 7.33−7.80 (m, 22H, aromatics), 8.22 (dd, 2H, $^3J_{H-H}$ = 6.0 Hz, $^3J_{P-H}$ = 6.50 Hz, *O*Ph).



(S_C, R_C/S_C)-**4**

Liberation of 1-(Diphenylphosphino)-2-(diphenylarsino)propane, (R_C)-5. The diastereomeric complex (S_C,R_C)-**4** (0.03 g) was added in dichloromethane (20 mL). This was then treated with potassium cyanide (1 g) in water (20 mL). The solution was stirred for 2 h at room temperature. After the two layers were settled, the aqueous layer was separated and the organic layer washed with water (3 × 20 mL). The solution was then washed with a diluted H_2SO_4 solution (3 × 15 mL, 0.5 M) to remove the naphthylamine auxiliary and then washed with water (3 × 20 mL). The solution was dried over $MgSO_4$ and then filtered off. After removal of the organic solvent, the chiral ligand (R_C)-**5** was isolated as a colorless oil, 0.15 g (90% yield). $[\alpha]_D$: +131.0 (*c* 0.2, CH_2Cl_2). ^{31}P NMR ($CDCl_3$): δ −20.5 (s). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.38 (d, 3H, $^3J_{H-H}$ = 6.9 Hz, AsCH*Me*), 1.97 (dt, 1H, $^2J_{H-P,H}$ = 12.6 Hz, $^3J_{H-H}$ = 5.1 Hz, PC*H*$_a$H$_b$), 2.25−2.35 (m, 1H, AsC*H*Me), 2.37−2.44 (m, 1H, PCH$_a$*H*$_b$), 7.2−7.48 (m, 20H, aromatics).

Crystal Structure Determination of (S_C,R_C)-4. Crystal data and a summary of the crystallographic analyses are given in Table 2. Diffraction data were collected at the Nanyang Technological University using a Bruker X8Apex diffractometer with Mo Kα radiation (graphite monochromator). All non-H atoms were refined anisotropically, while H atoms were introduced at a fixed distance from the C and were assigned fixed thermal parameters. The absolute configurations of the chiral complex was determined unambiguously using the Flack parameter.[18] An ORTEP plot of the complex with a numbering scheme is given in Figure 1.

Acknowledgment. We thank Nanyang Technological University for support of this research and also the Institute of Chemical and Engineering Sciences for a scholarship to M.L.B.

Supporting Information Available: Crystallographic data in CIF format for (S_C,R_C)-**4** This material is available free of charge via the Internet at http://pubs.acs.org.

IC0701561

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